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(54) **SKIN LIGHTENING COMPOSITIONS**

HAUTAUFHELLUNGSSZUSAMMENSETZUNGEN

COMPOSITIONS D'ECLAIRCISSEMENT DE LA PEAU

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(56) References cited:
**EP-A- 0 524 109 WO-A-95/23780
WO-A-96/14055 FR-A- 2 577 805**

EP 0 952 815 B1

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DescriptionTECHNICAL FIELD

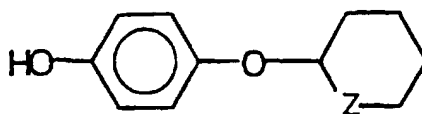
5 **[0001]** The present invention relates to the field of skin lightening. Specifically, the present invention relates to novel compositions comprising a liquid crystal which enhance skin penetration effect of specific hydroquinone derivatives for skin lightening.

BACKGROUND OF THE INVENTION

10 **[0002]** The specific hydroquinone as shown in formula (I) is known as a skin lightening compound. See WO9523780.

formula (I)

15



20

wherein Z is oxygen or sulfur.

25 **[0003]** The combination of the specific hydroquinone derivatives and penetration enhancers is disclosed in WO9523780.

[0004] WO9523780 describes that penetration enhancers are disclosed in Mahjour, M., B. Mauser, Z. Rashidbaigi & M.B. Fawzi, "Effect of Egg Yolk Lecithins and Commercial Soybean Lecithins on *In Vitro* Skin Permeation of Drugs", *Journal of Controlled Release*, Vol. 14 (1990), pp. 243-252. The journal discloses Lecithin as a penetration enhancer. However, there is no description of a liquid crystal comprising specific hydroquinone derivatives and lecithin which have penetration enhancing effect.

30 **[0005]** It is an object of the present invention to provide compositions for lightening mammalian skin which has a good penetration effect, so that the specific hydroquinone derivatives which are skin lightening actives can penetrate effectively and work effectively.

SUMMARY OF THE INVENTION

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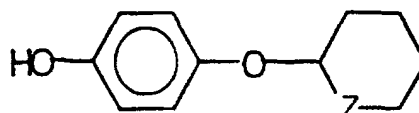
[0006] The present invention relates to a skin lightening composition comprising

(a) a safe and effective amount of a compound of formula (I)

40

{formula (I)}:

45



wherein Z is oxygen or sulfur.

50

(b) an average polarity solvent

(c) a polyhydric alcohol

(d) a solid fatty alcohol

(e) a nonionic surfactant

(f) water, and

55

(g) lecithin

wherein at least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The compound of the formula(I) have a good skin lightening effect in mammals, however it is expected to strengthen the penetration effect of the compound of formula (I) to mammal's skin. It has been unexpectedly found that the subject composition achieve good penetration in mammals' skin of the compounds of formula (I).

[0008] As used herein, "topical application" means directly laying on or spreading on outer skin.

[0009] As used herein, "skin lightening" means decreasing melanin in skin, including one or more of overall lightening of basal skin tone, lightening of hyperpigmented lesions including age spots, melasma, chloasma, freckles, post-inflammatory hyperpigmentation or sun-induced pigmented blemishes.

[0010] As used herein, "solid" means solid form at the temperature of 25 °C. and "liquid" means liquid form at the temperature of 25 °C.

[0011] As used herein, all percentages are by weight unless otherwise specified.

[0012] The typical examples of the compound of formula(I) is as follows.

4-[(tetrahydro-2H-pyran-2-yl)oxy]phenol (hereinafter called THPOP).

4-[(tetrahydro-2H-thiopyran-2-yl)oxy]phenol.

These compounds are produced by the method described in WO9523780.

[0013] A skin lightening composition of the present invention comprises preferably from about 0.001% to about 10%, more preferably from about 0.01% to about 8%, still more preferably from about 0.1% to about 5%, most preferably from about 0.5% to about 3% of the compound of the formula(I) as an active agent in a topical composition.

[0014] Use of subject compositions comprising over 3% of an active is preferred for lightening of hyperpigmented lesions and other areas where substantial lightening is desired.

Average Polarity Solvent

[0015] In order to dissolve the compounds of formula(I), since the compounds of formula(I) are molecules of average polarity being neither soluble in very polar solvents nor very non polar solvents, it is necessary to be dissolved in an average polarity solvent. The average polarity solvents could preferably be solvents which have the ratio of Organicity and Inorganicity (Organicity/Inorganicity) of 0.2 to 3.6, more preferably be solvents which have the ratio of Organicity and Inorganicity (Organicity/Inorganicity) of 0.5 to 3.5. The ratio of Organicity and Inorganicity (Organicity/Inorganicity) is described in Pharmaceutical Bulletin Vol. 2, No. 2, 163 (1954); and The Field of Chemical (Kagaku no Ryoiki) Vol. 11, No. 10, October 1957. The average polarity solvents include liquid triglycerides such as castor oil, olive oil, and capric/caprylic triglyceride; cosmetically acceptable ester oil such as isopropyl palmitate, oleyl oleate, 2-octyldodecyl myristate and neopentyl glycol dioctanoate (trade name: Cosmol 525 manufactured by Nisshin oil Mills LTD.); liquid fatty alcohols such as oleyl alcohol, isostearyl alcohol, lanolin alcohol, hexadecyl alcohol, octyldodecanol alcohol, linoleyl alcohol, linolenyl alcohol, arachidyl alcohol and 2-octyl dodecanol; liquid fatty acids such as oleic acid and iso-stearic acid; octyl methoxy cinnamate; cinoxate; and 2-ethylhexyl p-dimethylaminobenzoate. The following nonionic surfactants can be used as the average polarity solvents. Even if the following nonionic surfactants are used as the average polarity solvents, the other nonionic surfactants mentioned later (the "Nonionic surfactant" explanation pan in this specification) are necessary for the present invention. Nonionic surfactants as the average polarity solvents include ethers of polyoxypropylene or polyoxyethylene and aliphatic alcohol such as polyoxypropylene 15 stearyl ether and polyoxypropylene glycol 14 butyl ether; polyoxypropylene or polyoxyethylene castor oils or hydrogenated castor oils such as polyoxyethylene (3) castor oil and polyoxyethylene (5) hydrogenated castor oil; polyoxypropylene or polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene (20) sorbitan monooleate and sorbitan trioleate; polyoxypropylene or polyoxyethylene sorbit fatty acid esters such as polyoxyethylene (6) sorbitol tetraoleate; polyglycerin or glycerin fatty acid esters such as diglycerol monooleate, glycerol dioleate and glycerol monoisostearate; polyoxypropylene or polyoxyethylene glycerin fatty acid esters such as polyoxyethylene (5) glycerol monooleate; polyoxypropylene or polyoxyethylene alkyl phenyl ethers such as polyoxyethylene (2) nonylphenyl ether and polyoxyethylene (3) octylphenyl ether.

[0016] Among the average polarity solvents, either a liquid triglyceride or a cosmetically acceptable ester oil is preferred, and either capric/caprylic triglyceride or neopentyl glycol dioctanoate is more preferred. The good penetration effect is not obtained by the average polarity solvents per se but is obtained by said liquid crystal.

[0017] The amount of the average polarity solvents depend on the amount of the compounds of formula (I). However, the skin lightening composition of the present invention comprises preferably from 5% to 50% of the average polarity solvent, more preferably from 10% to 25% of the average polarity solvent.

[0018] Either one kind or two or more kinds of the average polarity solvent can be used in the present invention.

Polyhydric alcohol

5 [0019] Polyhydric alcohols include glycerin, diglycerin, triglycerin, polyglycerin, polypropylene glycol, polyethylene glycol, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, 1,4-butylene glycol, ethylene glycol monoalkyl ether, diethylene glycol monoalkyl ether, glucose, maltose, sucrose, lactose, xylitose, xylitol, sorbitol, mannitol, maltitol, malbit, panthenol, pentaerythritol, and hyaluronic acid and its salts.

Among the polyhydric alcohols, glycerin is preferred.

10 [0020] The skin lightening composition of the present invention comprises preferably from 0.1% to 10%, more preferably from 0.5% to 5% of the polyhydric alcohol.

[0021] Either one kind or two or more kinds of the polyhydric alcohol can be used in the present invention.

Solid fatty alcohol

15 [0022] Solid fatty alcohols include cetyl alcohol, stearyl alcohol, behenyl alcohol, myristyl alcohol, batyl alcohol, cholesterol and phytosterol.

Among the solid fatty alcohols, cetyl alcohol is preferred.

[0023] The skin lightening composition of the present invention comprises preferably from 0.1% to 10%, more preferably from 0.5% to 3% of the fatty alcohol.

20 [0024] Either one kind or two or more kinds of the solid fatty alcohol can be used in the present invention.

Nonionic surfactant

25 [0025] Nonionic surfactants include polyglycerin fatty acid esters, propylene glycol fatty acid esters, glycerin fatty acid esters, sorbitan fatty acid esters, sugar fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbit fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene glycerin fatty acid esters, polyoxyethylene castor oils, polyoxyethylene hardened castor oils, polyoxyethylene alkyl ethers, polyoxyethylene phytosterols, polyoxyethylene polyoxypropylene alkyl ethers, polyoxyethylene alkyl phenyl ethers, polyoxyethylene lanolins, polyoxyethylene lanolin alcohols, polyoxyethylene beeswax derivatives, polyoxyethylene fatty acid amides, polyether silicone derivatives, and polyoxyethylene fatty acid esters.

30 [0026] The nonionic surfactant could preferably be one which has HLB number of 10 to 17 and be solid at room temperature (25 °C). The preferable nonionic surfactants include polyoxyethylene(40) monostearate, polyoxyethylene (21) stearyl ether and decaglyceryl monostearate.

35 [0027] The skin lightening composition of the present invention comprises preferably from 0.1% to 5%, more preferably from 0.5% to 2% of the nonionic surfactant.

[0028] Either one kind or two or more kinds of the nonionic surfactant can be used in the present invention.

Water

40 [0029] The skin lightening composition of the present invention comprises preferably from 40% to 90%, more preferably from 60% to 80% of water.

Lecithin

45 [0030] Lecithin is a natural product derived from soybean or egg yolk.

[0031] The skin lightening composition of the present invention comprises preferably from 0.5% to 5%, more preferably from 2% to 3% of lecithin.

Combination Actives

50 A. Sunscreens and Sunblocks

[0032] Regulation of skin darkening resulting from exposure to ultraviolet light can be achieved by using combinations of the active skin lightening agents together with sunscreens or sunblocks. Useful sunblocks include, for example, zinc oxide and titanium dioxide.

55 [0033] Ultraviolet light is a predominant cause of skin darkening. Thus, for purposes of skin lightening, the combination of a skin lightening agent with a UVA and/or UVB sunscreen is desirable.

[0034] A wide variety of conventional suncreening agents are suitable for use in combination with the skin lightening

agent. Segarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology, disclose numerous suitable agents. Specific suitable sunscreens include, for example: p-aminobenzoic acid, its salts and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-aminobenzoates; methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, benzyl, menthyl, glyceryl, and dipropylene glycol esters); Cinnamic acid derivatives (menthyl and benzyl esters, butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxycinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); dihydroxy-naphthoic acid and its salts; o- and p-Hydroxybiphenyldisulfonates; coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); diazoles (2-acetyl-3-bromodiazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted benzophenones; uric and vilouric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carboto) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzone, sulisobenzone, dioxybenzone, benzoescorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropylidibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; and 4-isopropyl-di-benzoylmethane.

[0035] Of these, 2-ethylhexyl-p-methoxycinnamate, 4,4'-t-butyl methoxydibenzoyl-methane, 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid, digalloyltriolate, 2,2-dihydroxy-4-methoxybenzophenone, ethyl-4-(bis(hydroxypropyl)) aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexylsalicylate, glyceryl-p-aminobenzoate, 3,3,5-tri-methylcyclohexylsalicylate, methylanthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl-amino-benzoate, 2-phenylbenzimidazole-5-sulfonic acid, 2-(p-dimethylaminophenyl)-5-sulfonicbenzoxazonic acid and mixtures of these compounds, are preferred.

[0036] More preferred sunscreens useful in the compositions useful in the present invention are 2-ethylhexyl-p-methoxycinnamate, butylmethoxydibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid and mixtures thereof.

[0037] Also particularly useful in the compositions are sunscreens such as those disclosed in U.S. Patent No. 4,937,370 issued to Sabatelli on June 26, 1990, and U.S. Patent No. 4,999,186 issued to Sabatelli & Spirnak on March 12, 1991. The sunscreens disclosed therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultra-violet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range.

[0038] Preferred members of this class of sunscreens are 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl) methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N--(2-ethylhexyl) methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxy-ethoxy)benzophenone; 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane; N,N--di-(2-ethylhexyl)-4-aminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; and N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane and mixtures thereof.

[0039] A safe and effective amount of sunscreen may be used in the compositions useful in the present invention. The sunscreens agent must be compatible with the skin lightening agent. The composition preferably comprises from about 1% to about 20%, more preferably from about 2% to about 10%, of a sunscreens agent. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF).

[0040] An agent may also be added to any of the compositions useful in the present invention to improve the skin substantivity of those compositions, particularly to enhance their resistance to being washed off by water, or rubbed off. A preferred agent which will provide this benefit is a copolymer of ethylene and acrylic acid. Compositions comprising this copolymer are disclosed in U.S. Patent 4,663,157, Brock, issued May 5, 1987.

B. Anti-Inflammatory Agents

[0041] In a preferred skin lightening composition useful in the present invention, an anti-inflammatory agent is included as an active along with the skin lightening agent. The inclusion of an anti-inflammatory agent enhances the skin lightening benefits of the compositions. The anti-inflammatory agent protects strongly in the UVA radiation range (though it also provides some UVB protection as well). The topical use of anti-inflammatory agents reduces darkening of the skin resulting from chronic exposure to UV radiation. (See U.S. Patent 4,847,071, Bissett, Bush, and Chatterjee, issued July 11, 1989; and U.S. Patent 4,847,069, Bissett and Chatterjee, issued July 11, 1989.)

[0042] A safe and effective amount of an anti-inflammatory agent may be added to the compositions useful in the present invention, preferably from about 0.1% to about 10%, more preferably from about 0.5% to about 5%, of the composition. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

[0043] Steroidal anti-inflammatory agents, including corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, flucolorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, flucortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chlorprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucoloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred steroidal anti-inflammatory for use is hydrocortisone.

[0044] A second class of anti-inflammatory agents which is useful in the compositions includes the non-steroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc., of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K. D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, 1, R. A. Scherrer, et al., Academic Press, New York (1974).

[0045] Specific non-steroidal anti-inflammatory agents useful in the composition invention include:

- 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;
- 2) the salicylates, such as aspirin, disalcid, benorylate, trilsate, safapryn, solprin, diflunisal, and fendosal;
- 3) the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepiract, clidanac, oxepinac, and felbinac;
- 4) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;
- 5) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and
- 6) the pyrazoles, such as phenybutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

[0046] Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the pharmaceutically-acceptable salts and esters of these agents. For example, etofenamate, a flufenamic acid derivative, is particularly useful for topical application. Of the nonsteroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, and flufenamic acid are most preferred.

[0047] Another class of anti-inflammatory agents which are useful in the compositions are the anti-inflammatory agents disclosed in U.S. Patent No. 4,708,966, Loomans et al., issued November 24, 1987. This patent discloses a class of nonsteroidal anti-inflammatory compounds which comprise specifically substituted phenyl compounds, especially substituted 2,6-di-tert-butyl phenol derivatives. For example, compounds selected from 4-(4'-pentyn-3'-one)-2,6-di-tert-butylphenol; 4-(5'-hexynoyl)-2,6-di-tert-butylphenol; 4((S)-(-)-3'-methyl-5'-hexynoyl)-2,6-di-tert-butylphenol; 4-((R)-(+)-3'-methyl-5'-hexynoyl)-2,6-di-tert-butylphenol; and 4-(3',3'-dimethoxypropionyl)-2,6-di-tert-butylphenol are useful in methods of the present invention; 4-(5'-hexynoyl)-2,6-di-tert-butylphenol is most preferred.

[0048] Yet another class of anti-inflammatory agents which are useful in the compositions are those disclosed in U.S. Patent No. 4,912,248, Mueller, issued March 27, 1990. This patent discloses compounds and diastereomeric mixtures of specific 2-naphthyl- containing ester compounds, especially naproxen ester and naproxol ester compounds, having two or more chiral centers. For example, compounds selected from (S)-naproxen-(S)-2-butyl ester, (S)-naproxen-(R)-2-butylester, (S)-naproxol-(R)-2-methyl butyrate, (S)-naproxol-(S)-2-methyl butyrate, diastereomeric mixtures of (S)-naproxen-(S)-2-butyl ester and (S)-naproxen-(R)-2-butyl ester, and diastereomeric mixtures of (S)-naproxol-(R)-2-methyl butyrate and (S)-naproxol-(S)-2-methyl butyrate are useful in the present invention.

[0049] Finally, so-called "natural" anti-inflammatory agents are useful in methods of the present invention. For example, candelilla wax, alpha bisabolol, aloe vera, Manjistha (extracted from plants in the genus Rubia, particularly Rubia Cordifolia), and Guggal (extracted from plants in the genus Commiphora, particularly Commiphora Mukul), may be used

[0050] Another preferred composition useful in the present invention comprises a skin lightening agent, a sunscreen, and an anti-inflammatory agent together for skin lightening in the amounts disclosed for each individually hereinabove.

C. Anti-Oxidants/Radical Scavengers

[0051] In a preferred skin lightening composition useful in the present invention, an anti-oxidant/radical scavenger is included as an active along with the skin lightening agent. The inclusion of an anti-oxidant/radical scavenger increases the skin lightening benefits of the composition.

[0052] A safe and effective amount of an anti-oxidant/radical scavenger may be added to the compositions useful in the present invention, preferably from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition.

[0053] Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and its salts, tocopherol (vitamin E), tocopherol sorbate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the tradename Trolox[®]), gallic acid and its alkyl esters, especially propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, the ascorbyl esters of fatty acids, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl compounds (e.g., glutathione), and dihydroxy fumaric acid and its salts may be used.

[0054] In a preferred composition useful in the present invention, compositions comprise one, any two, or all three of a sunscreensing agent, anti-inflammatory agent, and/or an anti-oxidant/radical scavenging agent included as actives along with the skin lightening agent. The inclusion of two or all three of these agents with the skin lightening agent increases the skin lightening benefits of the composition.

D. Chelators

[0055] In a preferred composition useful in the present invention, a chelating agent is included as an active along with the skin lightening agent. As used herein, "chelating agent" means an active agent capable of removing a metal ion from a system by forming a complex so that the metal ion cannot readily participate in or catalyze chemical reactions. The inclusion of a chelating agent increases the skin lightening benefits of the composition.

[0056] A safe and effective amount of a chelating agent may be added to the compositions useful in the present invention, preferably from about 0.1% to about 10%. more preferably from about 1% to about 5%, of the composition. Chelators useful in compositions are disclosed in U.S. Patent Application Serial No. 619,805, Bissett, Bush & Chatterjee, filed November 27, 1990 (which is a continuation of U.S. Patent Application Serial No. 251,910, filed October 4, 1988); U.S. Patent Application Serial No. 514,892, Bush & Bissett, filed April 26, 1990; and U.S. Patent Application Serial No. 657,847, Bush, Bissett & Chatterjee, filed February 25, 1991. Preferred chelators useful in compositions of the present invention are furildioxime and derivatives thereof.

[0057] In a preferred composition useful in the present invention, compositions comprise one, any two, any three, or all four of a sunscreensing agent, anti-inflammatory agent, anti-oxidant/radical scavenging agent, and/or chelating agent included as actives along with the skin lightening agent. The inclusion of two, three, or all four of these agents with the skin lightening agent increases the skin lightening benefits of the composition.

E. Retinoids

[0058] In a preferred composition useful in the present invention, a retinoid, preferably retinoic acid, is included as an active along with the skin lightening agent. The inclusion of a retinoid increases the skin lightening benefits of the composition. A safe and effective amount of a retinoid may be added to the compositions useful in the present invention, preferably from about 0.001% to about 2%, more preferably from about 0.01% to about 1% of the composition. As used herein, "retinoid" includes all natural and/or synthetic analogs of Vitamin A or retinol-like compounds which possess the biological activity of Vitamin A in the skin as well as the geometric isomers and stereo isomers of these compounds, such as all-trans retinoic acid and 13-cis-retinoic acid.

[0059] In a preferred composition useful in the present invention, compositions comprise one, any two, any three, any four, and/or all five of a sunscreensing agent, anti-inflammatory agent, anti-oxidant/radical scavenging agent, chelating agent, and/or a retinoid included as actives along with the skin lightening agent. The inclusion of two, three, four, or all five of these agents with the skin lightening agent increases the skin lightening benefits of the composition.

Other Optional Components

[0060] Other optional components include thickeners such as carboxy vinyl polymer, preservatives, liquid and paste pigments, astringents, pH buffers, perfumes, infrared screening agents, amphoteric and solid amorphous lipids, vitamins, nutrients, and skin conditioning agents.

[0061] Useful skin conditioning agents are beta-glycyrrhetic acid and its derivatives, vegetation extracts, allantoin, collagen, and extract and treated elastin fibers.

[0062] The topical compositions useful in the present invention may be made into emulsion type product. These include milky lotions, creams and ointments.

[0063] The emulsion type product comprises a liquid crystal comprising the compound of formula (I), an average polarity solvent, a polyhydric alcohol, a fatty alcohol, a nonionic surfactant, water and lecithin.

[0064] Emulsions according to the present invention generally contain a cosmetically acceptable aqueous or organic solvent such as ethanol, isopropanol, sorbitol esters, and mixtures thereof and a lipid or oil. Lipids and oils may be derived from animals, plants, or petroleum and may be natural or synthetic (i.e., man-made).

[0065] The emulsion may also contain an anti-foaming agent to minimize foaming upon application to the skin. Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use.

[0066] The emulsions preferably comprise a silicone for imparting a preferred skin feel. Generally such silicones have a low molecular weight. Suitable such silicones include cyclomethicones, dimethicones, and blends such as Dow Corning 200 fluid (especially 10 cs) and Dow Corning Q2-1401. Such silicones are commercially available from the Dow Corning Corp. of Midland, MI.

[0067] The skin lightening composition of the present invention may comprise a topical cosmetically acceptable emollient. As used herein, "emollient" refers to a material used for the prevention or relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients are known and may be used herein. Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972) contains numerous examples of materials suitable as an emollient. The skin lightening cosmetic of the present invention typically comprises from about 5% to about 50%, preferably from about 10% to about 25%, of emollient.

Methods for Lightening Skin in Mammals

[0068] The present invention also relates to methods for skin lightening in mammals comprising topical application of the skin lightening composition of the present invention. The amount of active agent and frequency of application will vary widely depending upon the skin color already in existence in the subject, the rate of further darkening of the skin, and the level of lightening desired.

[0069] A safe and effective amount of skin lightening agent in a topical composition is applied, generally from about 1 g to about 10 g per cm² skin per application, preferably from about 2 g to about 8 g/cm² skin per application, more preferably from about 3 g to about 7 g/cm² skin, also preferably from about 4 g to about 5 g/cm² skin. Application preferably ranges from about four times a day to about twice a week, more preferably from about three times a day to about once every other day, more preferably still from about once daily to about twice daily. Application for at least five days is required to see a skin lightening effect in lower animals. Application for at least one month is required to see an effect in humans. After lightening is achieved, the frequency and dosage can be reduced to a maintenance level, as desired. Such maintenance varies according to the individual, but is preferably from about 1/10 to about 1/2, more preferably from about 1/5 to about 1/3 of the original dosage and/or frequency, as needed.

[0070] A preferred method of the present invention for skin lightening in mammals involves applying the skin lightening composition of the present invention further comprising a safe and effective amount of one or more of a sun-screening agent, an anti-inflammatory agent, an anti-oxidant/radical scavenging agent, a chelating agent and/or a retinoid. The amount of sun-screening agent applied is preferably from about 0.01 mg to about 0.1 mg per cm² skin. The amount of anti-inflammatory agent applied is preferably from about 0.005 mg to about 0.5 mg, more preferably from about 0.01 mg to about 0.1 mg per cm² skin. The amount of anti-oxidant/radical scavenging agent preferably applied is from about 0.01 mg to about 1.0 mg, more preferably from about 0.05 mg to about 0.5 mg per cm² skin. The amount of chelating agent preferably applied is from about .001 mg to about 1.0 mg, more preferably from about 0.01 mg to about 0.5 mg, still more preferably from about 0.05 mg to about 0.1 mg per cm² skin. The amount of retinoid applied is preferably from about 0.001 mg to about 0.5 mg per cm² skin, more preferably from about 0.005 mg to about 0.1 mg per cm² skin. The amount of skin lightening agent applied is preferably from about 0.001 mg to about 2 mg per cm² skin per application, more preferably from about 0.01 mg to about 1 mg per cm² skin per application.

Procedure for making a skin lightening composition of the present invention

[0071] For example, a skin lightening composition of the present invention which comprises a liquid crystal can be made by the steps of

- (i) mixing a safe and effective amount of a compound of the formula (I), an average polarity solvent, a fatty alcohol, a nonionic surfactant and lecithin at the temperature of 60 °C to 100 °C to obtain mixture 1, and
- (ii) mixing a polyhydric alcohol and water with the mixture 1 while maintained at the temperature of 45 °C to 100 °C.

[0072] The mixture obtained by the above steps (i) and (ii) is usually cooled to room temperature.

[0073] The other component can be mixed according to the convention manner, however, generally oil-soluble components can be added in the above step (i) and water-soluble components can be added in the above step (ii).

[0074] The liquid crystal can be detected by observing the shape of the liquid crystal by a polarization microscope.

5 EXAMPLES

[0075] The following examples further describe and demonstrate embodiments within the scope of the present invention.

10 Test Example 1

Procedure for making control composition

15 [0076] THPOP is dissolved in polypropylene glycol (14) butyl ether (THPOP phase-1) Separately, polyoxyethylene (21) stearyl alcohol, polyoxyethylene (2) stearyl alcohol, cetyl alcohol, stearyl alcohol, cyclomethicone and ascorbyl palmitate are dissolved at 70 °C and stirred well. The THPOP phase-1 is added thereto and mixed continuously. (THPOP phase-2)

In another vessel, all other ingredients than the above are dissolved at 70 °C. (water phase)

20 The THPOP phase-2 and the water phase are mixed well and allowed to cool to obtain oil-in-water emulsion (o/w emulsion). The components of control is shown in Table 1.

Procedure for making Test Composition No.1

25 [0077] THPOP, caprylic/capric triglyceride (Migyl 812), cetyl alcohol, polyoxyethylene(40) monostearate and lecithin are mixed together and heated to 70 °C. Then, deionized water and glycerin are added thereto with stirring and the mixture is emulsified. Then the emulsified mixture is cooled to room temperature with stirring to obtain an emulsion with a liquid crystal. The emulsion with the liquid crystal and all other ingredients than the above are mixed together to obtain Composition No.1. The component of composition No. is shown in Table 2.

30 Procedure for making Test Composition No.2

35 [0078] THPOP, neopentyl glycol dioctanoate (Cosmol 525), cetyl alcohol, polyoxyethylene(40) monostearate and lecithin are mixed together and heated to 70 °C. Then, deionized water and glycerin are added thereto with stirring and the mixture is emulsified. Then the emulsified mixture is cooled to room temperature with stirring to obtain an emulsion with a liquid crystal. The emulsion with the liquid crystal and all other ingredients than the above are mixed together to obtain Composition No.2. The component of composition No.2 is shown in Table 3.

Table 1

Control (Oil in Water emulsion)	
Component	Amount (weight%)
De-ionized water	75.70
Hydrochloric Acid IN	2.30
Triethanolamine	1.40
Mg Ascorbic Phosphate	0.10
Sodium Metabisulfite	0.05
Disodium EDTA	0.05
Polyoxyethylene (21) stearyl alcohol (21)	2.00
Polyoxyethylene (2) stearyl alcohol (2)	1.00
Polypropylene glycol (14) Butyl Ether	7.50
Cetyl Alcohol	3.00
Stearyl Alcohol	1.50
Cyclomethicone	1.00
Ascorbyl Palmitate	0.10
THPOP	3.00
Butylene glycol	1.00

EP 0 952 815 B1

Table 1 (continued)

Control (Oil in Water emulsion)	
Component	Amount (weight%)
Glydant Plus	0.30

("Glydant Plus" is Dimethylol-5,5- dimethylhydantoin (and) lodopropynyl Butyl carbamate)

Table 2

Composition No. 1	
Component	Amount (weight%)
Lecithin	3.00
Polyoxyethylene(40) monostearate (Myrj 52)	1.00
Cetyl Alcohol	1.00
Caprylic/Capric Triglyceride (Migylol 812)	15.00
D-delta Tocopherol	0.10
Glycerin	5.00
Propylparaben	0.10
Methylparaben	0.20
THPOP	3.00
De-ionized Water	69.13
Sodium Metabisulfite	0.08
Sodium Sulfite	0.20
Sodium Hydroxide	0.59
Carboxy vinyl polymer (Carbopol 980)	1.00
Benzyl Alcohol	0.60

Table 3

Composition No. 2	
Component	Amount (weight%)
Lecithin	3.00
Polyoxyethylene(40) monostearate (Myrj 52)	1.00
Cetyl Alcohol	1.00
Neopentyl glycol dioctoanate (Cosmol 525)	21.00
D-delta Tocopherol	0.10
Glycerin	5.00
Propylparaben	0.10
Methylparaben	0.20
THPOP	3.00
De-ionized Water	63.13
Sodium Metabisulfite	0.08
Sodium Sulfite	0.20
Sodium Hydroxide	0.59
Carboxy vinyl polymer (Carbopol 980)	1.00
Benzyl Alcohol	0.60

Test Method

(1) Apparatus

5 [0079] The unjacketed diffusion cell is used. The cross-sectional area for penetration is 0.79cm². This design is described by E.W. Merritt and E. R. Cooper, J. Controlled Release, 1(2), 161-162. Low glass tops that permit evaporation of the dose solution will be used for this study.

The diffusion cells are maintained at body temperature of 37 °C in aluminum blocks which sit in a stirring-heating module (Peirce Chemical Co.). Each aluminum block can accommodate six cells. The module controls the temperature and provides the stirring motor for the diffusion cells.

(2) Buffer Solution

15 [0080] The physiological saline solution used in this preparation is Dulbecco's phosphate buffered saline without calcium chloride and sodium bicarbonate (hereafter called "pbs") obtained from Wako Pure Chemical Industries LTD, CAM7276. Pbs is reconstituted with distilled water according to labeled instruction and 0.002% (s/v) sodium azide (Wako Pure Chemical Industries LTD, KCE 6293) is added to retard microbial growth. The pbs solution is maintained in a 37 °C water bath throughout the experiment in order to degas the solution. Evacuation of the solution using an aspirator, with stirring, for 15 minutes is also acceptable.

(3) Excised Human Cadaver Skin

25 [0081] Frozen excised human skin to a thickness of 0.25mm (following washing and hair clipping) can be obtained from the Ohio Valley Skin and Tissue Center (Shriners Burns Institute, Cincinnati, OH). Skin is bathed in a solution of broad-spectrum antibiotics for 24 hours, treated with a 10% glycerol solution, wrapped in gauze, and placed in sealed sterile foil packs. The skin is cut into ~1.2x1.2 cm² using a scalpel (Keisei Medical industrial Co., handle #4, blade #21). The receptor compartments of the glass diffusion cells, filled with pbs solution (4-5 ml), are maintained at 37 °C in the aluminum blocks. The squares are mounted horizontally onto the cells with the stratum corneum facing the donor compartment and the dermis in contact with the receptor compartment. Non-occluded glass tops are placed onto the cells and firmly clamped in place. The aluminum blocks are placed back into the modules and micro magnetic stir bars are put into the receptor compartments of the cells to continually stir throughout the course of the experiment.

(4) Experimental Methods

35 [0082] The skin is allowed to equilibrate overnight, or for a minimum of 16 hours, with the dermis in contact with pbs solution and the stratum corneum exposed to air. A basic computer program is used to randomize the treatment groups and each diffusion cell is labeled accordingly. Following equilibration and just prior to dosing, the solution in the receptor compartment is discarded and refilled with fresh pbs solution. This procedure consists of pouring out the solution in the receptor compartment, rinsing with 2-3 ml of fresh pbs solution and refilling with fresh pbs solution. When pouring out solution, a gloved hand containing a magnet is used to prevent the micro stir bar from being expelled. Air bubbles which collect on the dermal surface of the skin are removed by holding the glass cell at an angle and gently tapping. Temperature of the solution in the receptor compartment is randomly observed, and adjusted if necessary, throughout the course of the experiment using a SATO PAC-9400 thermocouple thermometer.

(5) Dosing and Sampling Procedures

45 [0083] Test compositions and controls are dosed onto the stratum corneum (donor compartment) using a pipettor. If a small volume of material is dosed, the pipette tip is used to distribute the material evenly over the skin. If occlusion is called for, a small piece of parafilm is placed over the glass top immediately following dosing. Receptor compartment samples are usually collected 6 and 24 hours post-dose. Sampling consists of pouring the solution from the receptor compartment into a vial, rinsing with 2-3 ml of pbs solution and adding this rinse to the vial, then refilling with fresh pbs solution. Blank samples (pbs solution only) are obtained after each collection period and used for the background determination. Dummy dosing solution aliquots are weighed into scintillation vials for HPLC analysis in order to calculate the average dose applied to each cell. Aliquots from a prepared solution of test material and ethanol are also submitted for HPLC analysis to standardize the results and establish a conversion factor for the data analysis.

(6) Cleaning Procedures

[0084] At the end of the experiment, cells are dismantled and washed in a strong detergent solution (Alconox), rinsed with distilled water and allowed to air dry. Skin is wrapped in foil and stored in the freezer prior to disposal by incineration. In case of lacking incineration facility, a concentrated H₂SO₄ bath can be used to dissolve skin. Stir bars are rinsed and placed overnight in a beaker containing ethanol. Clamps are rinsed in distilled water and occasionally washed in an Alconox solution.

(7) HPLC Analysis

[0085] The penetration samples and aliquots of dosing and standard solutions are then analyzed for THPOP% by HPLC, (High Performance Liquid Chromatography -Shimazu LC-9A using JSPHERE ODS M80 Column)

[0086] Penetration value was calculated by the following equation.

Penetration value(%)=

$$\frac{\text{penetrated amount of THPOP at each time point(mg)}}{\text{amount of THPOP in applied composition(mg)}} \times 100$$

[0087] The test result is shown in Table 4.

Table 4

Tested composition	Penetration value (%) in each time	
	6 hrs	24 hrs
Composition No.1	5.20	18.07
Composition No.2	6.47	23.92
Control	2.94	6.54

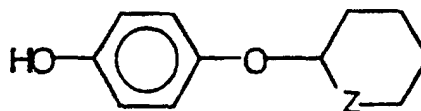
[0088] As shown in the above Table 4, excellent penetration enhancing effect can be obtained by the composition No.1 and the composition No.2 of the present invention.

Claims

1. A skin lightening composition comprising

(a) a safe and effective amount of a compound of the formula (I)

[formula (I)]:



wherein Z is Oxygen or Sulfur,

- (b) an average polarity solvent
- (c) a polyhydric alcohol
- (d) a solid fatty alcohol
- (e) a nonionic surfactant
- (f) water, and
- (g) lecithin

wherein at least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

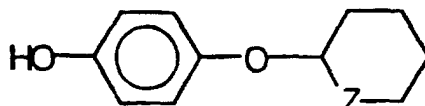
2. A skin lightening composition comprising by weight to the entire composition

(a) 0.001-10% of a compound of the formula (1)

5

[formula (1)]:

10



wherein Z is Oxygen or Sulfur.

15

(b) 5-50% of an average polarity solvent

(c) 0.1-10% of a polyhydric alcohol

(d) 0.1-10% of a solid fatty alcohol

(e) 0.1-5% of a nonionic surfactant

(f) 40-90% of water, and

(g) 0.5-5% of lecithin

20

wherein at least a portion of the above components (a), (b), (c), (d), (e), (f) and (g) forms a liquid crystal.

3. The composition of Claim 2 wherein Z is Oxygen.

4. The composition of Claim 2 wherein Z is Sulfur.

25

5. The composition of Claim 2 wherein the compound of the formula (1) is dissolved in the average polarity solvent.

6. The composition of Claim 2 wherein the average polarity solvent has the ratio of Organicity and Inorganicity of 0.2 to 3.6.

30

7. The composition of Claim 2 wherein the average polarity solvent is a liquid triglyceride.

8. The composition of Claim 2 wherein the average polarity solvent is a cosmetically acceptable ester oil.

35

9. The composition of Claim 2 wherein the average polarity solvent is capric/caprylic triglyceride.

10. The composition of Claim 2 wherein the average polarity solvent is neopentyl glycol dioctanoate.

11. The composition of Claim 2 wherein the polyhydric alcohol is glycerin.

40

12. The composition of Claim 2 wherein the solid fatty alcohol is cetyl alcohol.

13. The composition of Claim 2 wherein the nonionic surfactant has HLB of 2 to 20.

45

14. The composition of Claim 2 wherein the nonionic surfactant is polyoxyethylene(40) monostearate.

15. The composition of Claim 2 wherein the composition is a topical composition.

16. An emulsion composition which comprises said liquid crystal according to Claim 2.

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17. A cream composition which comprises said liquid crystal according to Claim 2.

18. A method for skin lightening in mammals which comprises topical application of skin lightening composition according to Claim 1.

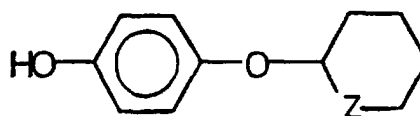
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19. A process for preparing a skin lightening composition comprising a liquid crystal which comprises the steps of

(i) mixing by weight to the entire composition

(a) 0.001-10% of a compound of the formula (I)

[formula (I)]:



wherein Z is Oxygen or Sulfur,

(b) 5-50% of an average polarity solvent

(c) 0.1-10% of a solid fatty alcohol

(d) 0.1-5% of a nonionic surfactant, and

(e) 0.5-5% of lecithin

at the temperature of 60 °C to 100 °C to obtain mixture 1, and

(ii) mixing with the mixture 1 by weight to the entire composition

(f) 0.1-10% of a polyhydric alcohol, and

(g) 40-90% of water

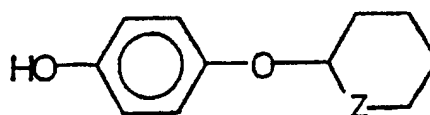
while maintained at the temperature of 45 °C to 100 °C.

Patentansprüche

1. Hautaufhellungszusammensetzung, umfassend

(a) eine sichere und wirksame Menge einer Verbindung der Formel (I)

[Formel (I)]:



worin Z Sauerstoff oder Schwefel ist,

(b) ein Lösungsmittel durchschnittlicher Polarität

(c) einen mehrwertigen Alkohol

(d) einen festen Fettalkohol

(e) ein nicht-ionisches grenzflächenaktives Mittel

(f) Wasser, und

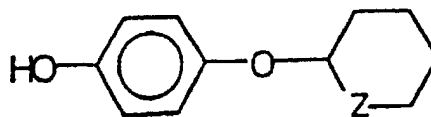
(g) Lecithin,

worin mindestens ein Teil der vorgenannten Komponenten (a), (b), (c), (d), (e), (f) und (g) einen Flüssigkristall bildet.

2. Hautaufhellungszusammensetzung, umfassend, bezogen auf das Gewicht der gesamten Zusammensetzung,

(a) 0,001-10% einer Verbindung der Formel (I)

[Formel (I)]:



- 10 worin Z Sauerstoff oder Schwefel ist,
 (b) 5-50% eines Lösungsmittels durchschnittlicher Polarität
 (c) 0,1-10% eines mehrwertigen Alkohols
 (d) 0,1-10% eines festen Fettalkohols
 (e) 0,1-5% eines nicht-ionischen, grenzflächenaktiven Mittels
 15 (f) 40-90% Wasser und
 (g) 0,5-5% Lecithin,
 worin mindestens ein Teil der vorgenannten Komponenten (a), (b), (c), (d), (e), (f) und (g) einen Flüssigkristall bildet.
- 20 3. Zusammensetzung nach Anspruch 2, worin Z Sauerstoff ist.
4. Zusammensetzung nach Anspruch 2, worin Z Schwefel ist.
- 25 5. Zusammensetzung nach Anspruch 2, worin die Verbindung der Formel (I) in dem Lösungsmittel durchschnittlicher Polarität gelöst ist.
6. Zusammensetzung nach Anspruch 2, wobei das Lösungsmittel durchschnittlicher Polarität ein Verhältnis von Organischem und Anorganischem von 0,2 bis 3,6 aufweist.
- 30 7. Zusammensetzung nach Anspruch 2, wobei das Lösungsmittel durchschnittlicher Polarität ein flüssiges Triglycerid ist.
8. Zusammensetzung nach Anspruch 2, wobei das Lösungsmittel durchschnittlicher Polarität ein kosmetisch verträgliches Esteröl ist.
- 35 9. Zusammensetzung nach Anspruch 2, wobei das Lösungsmittel durchschnittlicher Polarität Caprin/Capryl-Triglycerid ist.
10. Zusammensetzung nach Anspruch 2, wobei das Lösungsmittel durchschnittlicher Polarität Neopentylglycoldioctanoat ist.
- 40 11. Zusammensetzung nach Anspruch 2, wobei der mehrwertige Alkohol Glycerin ist.
12. Zusammensetzung nach Anspruch 2, wobei der feste Fettalkohol Cetylalkohol ist.
- 45 13. Zusammensetzung nach Anspruch 2, wobei das nicht-ionische grenzflächenaktive Mittel eine HLB von 2 bis 20 aufweist.
14. Zusammensetzung nach Anspruch 2, wobei das nicht-ionische grenzflächenaktive Mittel Polyoxyethylen(40)monostearat ist.
- 50 15. Zusammensetzung nach Anspruch 2, wobei die Zusammensetzung eine topische Zusammensetzung ist.
16. Emulsionszusammensetzung, welche den Flüssigkristall nach Anspruch 2 umfaßt.
- 55 17. Cremezusammensetzung, welche den Flüssigkristall nach Anspruch 2 umfaßt.
18. Verfahren zur Hautaufhellung in Säugern, welches die topische Anwendung der Hautaufhellungszusammensetzung

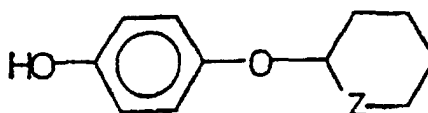
zung nach Anspruch 1 umfaßt.

19. Verfahren zur Herstellung einer Hautaufhellungszusammensetzung, umfassend einen Flüssigkristall, welches die Schritte umfaßt

(i) Mischen, bezogen auf das Gewicht der gesamten Zusammensetzung,

(a) 0,001-10% einer Verbindung der Formel (I)

[Formel (I)]:



worin Z Sauerstoff oder Schwefel ist,

(b) 5-50% eines Lösungsmittels durchschnittlicher Polarität

(c) 0,1-10% eines festen Fettalkohols

(d) 0,1-5% eines nicht-ionischen, grenzflächenaktiven Mittels

(e) 0,5-5% Lecithin und

bei der Temperatur von 60°C bis 100°C zum Erhalten eines Gemisches I und

(ii) Mischen von

(f) 0,1-10% eines mehrwertigen Alkohols und

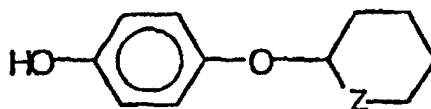
(g) 40-90% Wasser,

bezogen auf das Gewicht der gesamten Zusammensetzung, mit dem Gemisch I unter Beibehalten der Temperatur von 45°C bis 100°C.

Revendications

1. Composition d'éclaircissement de la peau comprenant :

(a) une quantité sûre et efficace d'un composé de formule [(I)]



dans laquelle Z est un oxygène ou du soufre,

(b) un solvant polarité moyenne

(c) un alcool polyhydrique

(d) un alcool gras solide

(e) un tensioactif non ionique

(f) de l'eau, et

(g) de la lécithine
dans laquelle au moins une partie des composés précédents (a), (b), (c), (d), (e), (f) et (g) forment un cristal
liquide

- 5 **2.** Composition d'éclaircissement de la peau comprenant, en poids par rapport à la composition entière,
- (a) de 0,001 à 10 % d'un composé de formule (I) [formule I]
 dans laquelle Z est un oxygène ou un soufre,
- 10 (b) de 5 à 50 % d'un solvant à polarité moyenne
- (c) de 0,1 à 10 % d'un alcool polyhydrique
- (d) de 0,1 à 10 % d'un alcool gras solide
- 15 (e) 0,1 à 5 % d'un tensioactif non ionique
- (f) 40 à 90 % d'eau, et
- 20 (g) 0,5 à 5 % de lécithine
 dans laquelle au moins une partie des composants précédents a), (b), (c), (d), (e), (f) et (g) forment un cristal
 liquide.
- 25 **3.** Composition selon la revendication 2., dans laquelle Z est un oxygène.
- 4.** Composition selon la revendication 2., dans laquelle Z est un soufre
- 5.** Composition selon la revendication 2., dans laquelle le composé de la formule I est dissout dans le solvant à
 polarité moyenne.
- 30 **6.** Composition selon la revendication 2., dans laquelle le solvant à polarité moyenne a comme rapport d'organicité
 et d'inorganicité de 0,2 à 3,6.
- 7.** Composition selon la revendication 2., dans laquelle le solvant à polarité moyenne est un triglycéride liquide.
- 35 **8.** Composition selon la revendication 2., dans laquelle le solvant à polarité moyenne est une huile d'ester cosméti-
 quement acceptable.
- 9.** composition selon la revendication 2, dans laquelle le solvant à polarité moyenne est un triglycéride caprique/
 caprylique.
- 40 **10.** Composition selon la revendication 2, dans laquelle le solvant à polarité moyenne est le néopentyl glycole dioc-
 taoanate.
- 45 **11.** Composition dans laquelle l'alcool polyhydrique est la glycérine.
- 12.** Composition selon la revendication 2, dans laquelle l'alcool gras solide est l'alcool cétylique.
- 13.** Composition selon la revendication 2, dans laquelle le tensioactif non ionique possède une HLB de 2 à 20.
- 50 **14.** Composition selon la revendication 2, dans laquelle le tensioactif non ionique est le polyoxyéthylène (40) monos-
 téarate.
- 15.** Composition selon la revendication 2, dans laquelle la composition est une composition locale.
- 55 **16.** Composition d'émulsion qui comprend ledit cristal liquide en conformité avec la revendication 2.
- 17.** Composition de crème qui comprend ledit cristal liquide en conformité avec la revendication 2.

18. Procédé d'éclaircissement de la peau chez des mammifères qui comporte l'application locale de la composition d'éclaircissement de la peau en conformité avec la revendication 1.

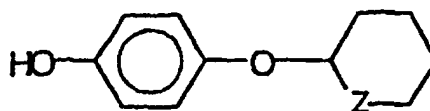
5 19. Procédé de préparation d'une composition d'éclaircissement de la peau comportant un cristal liquide qui comprend les étapes de

(i) mélange en poids de la composition entière

10 (a) 0,001 à 10 % d'un, composé de formule (I)

[formule (I)]

15 (a) (v)



25 dans laquelle Z est un oxygène ou un soufre,

(b) 5 à 50 % d'un solvant à polarité moyenne

30 (c) 0,1 à 10 % d'un alcool gras solide

(d) 0,1 à 5 % d'un tensioactif non ionique, et

(e) 0,5 à 5 % de lécithine

à la température de 60° C à 100° C pour obtenir le mélange 1, et

35 (ii) mélange du mélange 1 en poids à la composition entière

(f) 0,1 à 10 % d'un polyhydrique, et

40 (g) 40 à 90 d'eau

tout en le maintenant à la température de 45° C à 100° C.